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APPLICATION NO. 07/107,100	FILING DATE 11/07/00	FIRST NAMED INVENTOR MORGAN	ATTORNEY DOCKET NO. 07-107,100-1
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EXAMINER REVISED

ART UNIT 1001	PAPER NUMBER
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DATE MAILED:

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07/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/207,188

Applicant(s)

Blake et al.

Examiner

S. Devi, Ph.D.

Group Art Unit

1645

☒ Responsive to communication(s) filed on 01/07/2000.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 61-79 ~~is/are~~ are pending in the application.

Of the above, claim(s) 73-79 ~~is/are~~ are withdrawn from consideration.

☒ Claim(s) 1-60 ~~is/are~~ are ~~rejected~~ ^{canceled}.

☒ Claim(s) 61-72 ~~is/are~~ are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5.

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Change of Art Unit Location

1) Effective 20 June 2000, the Art Unit location of your application in the US PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1645.

Priority

2) The instant application is a Continuation of application, SN 08/231,229, filed 04/21/94, now US patent 5,866,135.

Preliminary Amendment

3) Acknowledgment is made of Applicants' preliminary amendment filed 03/31/99 (paper no. 2), which amendment has been entered.

Election

4) Acknowledgment is made of Applicants' election, with traverse (filed 01/07/2000 - paper no. 4) of invention I, claims 61-72, set forth in the restriction requirement mailed 12/08/99 (paper no. 3). Elected claims are drawn to a method of immunizing a mammal against group A streptococcal infection by administering a polysaccharide of formula I covalently linked to a protein.

The Applicants' traversal, in essence, is on the grounds that the polysaccharide formula I is a unifying element of all claims and therefore, it is not a serious burden on the Examiner to examine the claims as a whole.

The Applicants' argument has been fully considered, but is not persuasive. As clearly set forth in the restriction requirement mailed 12/08/99 (paper no. 3), the method of invention I accomplishes active immunization using a polysaccharide-protein conjugate and thus differs from the method of invention III which accomplishes passive immunization using an antibody product which is structurally, functionally and biologically distinct from the conjugate product used in the method of invention I. The two methods clearly differ in the compositions used and ultimate goals accomplished and thus are classified in different subclasses. Furthermore, the product used in invention I belongs to class 424, whereas the product used in invention III belongs to class 530.

Serial Number 09/207,188
Art Unit: 1645

Invention II is drawn to an immune composition comprising antibodies that are not required to practice the method of invention I. Thus, the elected group, invention I, is unrelated to inventions I and II and a search performed for the method of invention I would not be complete and co-extensive for the method of invention III. Therefore, the restriction requirement set forth in the action mailed 12/08/99 (paper no. 3) is proper and is hereby made FINAL.

Status of Claims

- 5) Claims 1-60 have been canceled via the preliminary amendment filed 03/31/99 (paper no. 2).

New claims 61-79 were added via the preliminary amendment filed 03/31/99 (paper no. 2).
are pending.

Claims 61-79 are pending in this application.

Claims 73-79 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 61-72 have been elected via the response to restriction requirement filed 01/07/99 (paper no. 4) and are under examination. An Action on the Merits for these claims is issued.

Information Disclosure Statement

- 6) Acknowledgment is made of Applicants' Information Disclosure Statement filed 12/08/1998 (paper no. 1). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 7).

Drawings

- 7) The drawings are objected to under 37 C.F.R 1.84 because of the reasons set forth by the Draftsperson in the attached Form PTO 948 (paper no. 7). Correction is required.

Abstract

- 8) The abstract of the instant specification is objected to because it contains more than one paragraph. Correction is required.

Specification - Informalities

- 9) The specification is objected to for the following reasons:
(a) The instant specification does not provide the priority/continuity information and

the status of the earlier filed application in the first paragraph of the specification. Amendment to the specification is suggested to provide the details and the current issued status of the parent application as indicated in paragraph 1 above.

(b) Figures 1 and 4 have two and three panels respectively. These panels are referred to in the drawings and in the specification as panels, A and B, and A, B and C respectively, instead of being referred to as: Figures 1A and 1B, and Figures 4A, 4B and 4C respectively. Further, the 'Brief Description of the Drawings' for Figures 1 and 4 on pages 7 and 8 of the specification do not properly refer to these panels as Figures 1A and 1B, and Figures 4A, 4B and 4C. Correction is requested.

(c) On page 11, lines 14 and 15 and page 12, line 31, the address of the American Type Culture Collection is incorrect. Effective 23 March 1998, ATCC has a new address: 10801 University Boulevard, Manassas, VA 20110-2209. Amendment to the specification is suggested to reflect this.

(d) The specification on page 11, lines 12-15 states that cultures of group A variant *Streptococcus* that produce the polysaccharide of the invention are deposited at the American Type Culture Collection. However, the specification is missing the specific accession number given by the depository to this variant strain without which one of ordinary skill in the art would not be able to practice the invention. It is suggested that Applicants amend the specification provide the missing accession number of the strain.

Rejections under 35 U.S.C. § 112, Second Paragraph

10) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

11) Claims 61-72 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 61 is vague in the recitation of "a number from about 3 to about 30" (see last two lines), because it is unclear what is encompassed in the limitation "about". Is the number 1 or 40 encompassed in this range? Can the limitation "about" be interpreted as " ± 10 or ± 20 "?

Clarification is requested.

(b) Claim 62 lacks antecedent basis for the recitation "**the** group A polysaccharide" (Emphasis added) (see lines 2 and 3), because claim 62 depends from claim 61 which does not recite any "group A polysaccharide", but "the polysaccharide of formula I".

(c) Claim 63 is vague in the recitation of "an amount of about 0.10 μg to about 10 μg " (see line 2) because it is unclear what is encompassed in the limitation "about". The metes and bounds of the recitation "about" are indeterminate. Is an amount of 0.001 μg or 20 μg encompassed in this range? Clarification is requested.

(d) Claim 62 is vague in the recitation of "about 10 Kd" (see line 2) because it is unclear what is encompassed in the limitation "about". The metes and bounds of the recitation "about" are indeterminate. Can the limitation "about" be interpreted as " ± 10 or ± 20 "? Clarification is required.

(d) Claim 67 lacks antecedent basis for the recitation "**the** polysaccharide-protein **conjugate**" (lines 1 and 2) (Emphasis added). Claim 67 depends from claim 66, which depends from 65, which depends from 64, which in turn depends from claim 61, none of which recite any "conjugate".

(e) Claim 68 lacks proper antecedent basis for the recitation "wherein polysaccharide is" (see line 1). For proper antecedent basis, it is suggested that Applicants replace the recitation with --wherein the polysaccharide is--.

Rejection(s) under 35 U.S.C. § 102

12) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13) Claims 61-63, 68 and 69 are rejected under 35 U.S.C. § 102(b) as being anticipated by Reimer *et al.* (Carbohydr. Res. 232: 131-142, 1992 - Applicants' IDS).

Reimer *et al.* teach a method of immunizing a rabbit (i.e., a mammal) by administering 0.1 mL (i.e., an immunogenic amount) of a Group A streptococcal oligosaccharide covalently linked

or conjugated to a protein, such as, bovine serum albumin or BSA (see abstract, and the first full paragraph on page 133). The oligosaccharide may be a branched trisaccharide or pentasaccharide (see abstract). The structure of the oligosaccharide is depicted on pages 135 and 141. The molecular weight of 10 Kd is inherent to the oligosaccharide of the prior art. The amount of 0.1 mL per rabbit of the glycoconjugate used for immunization is obtained from a solution containing 12 mg of the glycoconjugate in 12 mL of phosphate buffered saline and Freund's Complete adjuvant (see the first full paragraph on page 133) and therefore, falls in the dosage amount of about 0.10 to about 10 micrograms per kilogram of body weight recited in claim 63.

Claims 61-63, 68 and 69 are anticipated by Reimer *et al.*

Rejection(s) - 35 U.S.C. § 103

14) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

15) Claims 61-72 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Reimer *et al.* (*Carbohydr. Res.* 232: 131-142, 1992 - Applicants' IDS) in view of Jennings *et al.* (US 4,356,170) and Barnes *et al.* (WO 87/06590).

The teachings of Reimer *et al.* are described above which do not disclose the use of a bacterial protein such as tetanus toxoid or diphtheria toxoid in the Group A streptococcal conjugate used in their method of immunization, the use of an adjuvant selected from the group

recited in claim 70 and immunizing a human or human child with their conjugate.

However, Jennings *et al.* teach the use of carbohydrates from beta-hemolytic Group A streptococci for the purpose of conjugation to a protein carrier, such as, tetanus toxoid and diphtheria toxoid (see column 3, lines 15-22 and 45-55). The polysaccharide is coupled to the protein via a free amino group (see column 3, last paragraph). The use of conjugate vaccines in human infants and the use of adjuvants including aluminum hydroxide, aluminum sulfate, aluminum phosphate or an alum is specifically disclosed (see column 4). The molecular weight of the polysaccharide disclosed is 10,000 (i.e., 10 Kd) (see column 4, lines 50-60), or can be within 2000-100,000 (see column 4, lines 21 and 22). The immunization protocol is disclosed in columns 6 and 7. The dosage ranges from 5 to 25 micrograms (see column 4, lines 40-44).

Barnes *et al.* disclose the disadvantages of using Freund's complete adjuvant for *in vivo* use. Barnes *et al.* teach that when used with an antigen in an injectable form, large lesions often form at the site of injection, which render the adjuvant unsatisfactory for use in humans, pets and in meat animals (see page 1, fourth full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the BSA protein carrier in the Reimer's Group A streptococcal oligosaccharide-protein glycoconjugate used in Reimer's method of immunization of a mammal, with Jennings' medically useful protein carrier, such as, tetanus toxoid or diphtheria toxoid, and substitute Reimer's Freund's Complete adjuvant with Jennings' aluminum hydroxide or aluminum phosphate, to produce the instant invention, with a reasonable expectation of success. One skilled in the art would have been motivated to make the substitutions for the expected benefit of having a clinically more useful, microbial protein carrier than BSA in the conjugate and a clinically acceptable, less toxic adjuvant than Freund's Complete adjuvant for use in Reimer's method of immunization, since Barnes *et al.* teach that Freund's Complete adjuvant is unsatisfactory for human use because it causes large lesions at the site of injection.

Claims 61-72 are *prima facie* obvious over the prior art of record.

Objections(s) to Claims

16) Claims 61, 63 and 70 are objected for the reasons given below:

(a) Claim 61 is objected to for recitation "to protein" (see last line) without a

preceding article in between. It is suggested that Applicants replace the recitation with --to a protein-- to obviate the rejection.

(b) Claim 70 is objected to for the use of an abbreviation "QS21" in the claim language. It is suggested that the abbreviation be recited as a full terminology at first occurrence, with its abbreviated recitation retained in parentheses.

State of the Art

17) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicant's disclosure:

- Michon *et al.* (*In: VI International Congress for Infectious Diseases*, Prague, Czech Republic, April 26-30, 1994, abstract) teach a glycoconjugate vaccine comprising the polysaccharide of Group A streptococci conjugated through its reducing end to tetanus toxoid (TT) by reductive amination. A method of actively immunizing the rabbits with the conjugate to induce polysaccharide-specific, opsonophagocytic antibodies and a method of passive immunization using conjugate-induced serum to confer protection against group A streptococcal challenge are taught (see abstract).
- Pinto *et al.* (*Carbohydr. Res.* 210: 199-219, 1991) teach glycoconjugates comprising Group A beta-hemolytic streptococcal branched trisaccharide and pentasaccharide conjugated with a protein carrier such as bovine serum albumin (see abstract; pages 208 and 218, and Scheme 5). The glycoconjugates are used as immunizing agents in the generation of hybridoma (see the sentence bridging pages 208 and 209).
- Albernas *et al.* (*Carbohydr. Res.* 245: 245-257, 1993) teach a trisaccharide and hexasaccharide of the cell wall polysaccharide of the beta hemolytic Group A streptococci and the polysaccharide of the formula I (see abstract and page 247).
- Garegg *et al.* (*Acta Chem. Scand.* B 36: 25-26, 1982) teach a fragment of Group A Streptococcal cell wall polysaccharide coupled to a protein and the antigenic properties of the conjugate (see page 65).
- Pinto *et al.* (*ACS Symposium Series* 519: 111-131, Chapter 9, 1992) teach that only the antibodies raised to the group A streptococcal cell wall pentasaccharide cross-reacts with the native Group A streptococcal polysaccharide suggesting that an extended epitope is being

Serial Number 09/207,188
Art Unit: 1645

recognized by the polyclonal antisera raised against the branched pentasaccharide conjugate (see page 128).

Remarks

- 18) Claims 61-72 stand rejected.
- 19) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.
- 20) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 a.m to 4.00 p.m. A message may be left on the Examiner's voice mail service.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynnette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD
S. Devi
July 2000